PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Process for Producing Cycloalkyl-arylketones

We, SOCIETA EDISON, a Corporation of the Republic of Italy, of Foro Bonaparte 31, Milan, Italy, an Italian body corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

THE PRESENT INVENTION relates to a process for obtaining cycloaliphatic-aromatic ketones and more particularly relates to a process for obtaining cycloalkylaryl-ketones starting from aromatic hydrocarbons and cycloaliphatic-carboxylic acids.

It is known that ketones may be prepared by means of the Friedel-Craft reaction, by reacting aromatic hydrocarbons with carboxylic acids or their derivatives, such as for instance chlorides and anhydrides, in the presence of catalysts such as anhydrous aluminum-trichloride which is the condensing agent most commonly used. Though aluminum-trichloride has a catalytic function only, in order to obtain good yields of ketones, it is necessary to use great quantities of it. For instance, when using carboxylic acid as acylating agent 5—6 moles of aluminium trichloride are required per mole of acid. Besides, these known methods present the considerable drawback that it is impossible to recover the aluminum chloride used in the reaction, so that the process is uneconomical, especially when applied on an industrial scale. Another drawback of the condensing agents generally used in the known condensation-processes, is that they present a considerable corrosion with respect to the materials used for the construction of industrial plant.

The present invention provides an industrial process allowing the preparation of cycloalkyl-aromatic ketones starting from aromatic-hydrocarbons and cycloalkanecarboxylic acids, without having to resort to the use of acid anhydrides or acyl halides which are considerably less economical products than free carboxylic acids.

This invention uses polyphosphoric acid as a condensing agent without harmful secondary reactions taking place.

In this process the condensing agent used is easily recoverable and the condensing agent does not cause any corrosion of the materials used in the construction of the plant.

The invention consists in a process for preparing cycloalkyl aryl ketones in which an aromatic hydrocarbon is reacted with a cycloalkane carboxylic acid in the presence of polyphosphoric acid having a total content of phosphoric anhydride between 73 and 88% by weight, at such a temperature that the polyphosphoric acid is to some extent fluid.

The process of this invention may be schematically represented as follows:—

$$Ar-H+R-COOH \longrightarrow Ar-CO-R+H_2O$$

wherein Ar represents a radical of an aromatic hydrocarbon and R represents a radical of a cycloaliphatic hydrocarbon preferably having e.g. a ring of from 4 to 12 carbon atoms.

Examples of aromatic hydrocarbons suitable for carrying out this invention are: benzene, toluene, xylenes, ethylbenzene and cumene.

Examples of cycloaliphatic-carboxylic acids which can be used in the process of the present invention are: cyclopentanecarboxylic acid, hexahydrobenzoic acid, cyclooctane-carboxylic acid, cyclohendecanecarboxylic acid, cyclododecanecarboxylic acid, as well as their alkyl-substituted derivatives, for instance: 4-methyl-cyclohexanecarboxylic acid.

The polyphosphoric acid used as condensing agent in the process subject of this invention may be obtained according to the known conventional methods; i.e. by prolonged heating of orthophosphoric acid until the desired concentration in phosphoric anhydride is reached, or by dissolving the requisite amount of phosphoric anhydride in orthophosphoric acid. The polyphosphoric

acid is very complex and contains a mixture of orthophosphoric acid, pyrophosphoric and linear polyphosphoric acid.

The total content of phosphoric anhydride in the polyphosphoric acid used in the process of this invention lies between 73% and 88% and preferably between 80 and 85%, all proportions by weight. The temperature at which the process according to this invention is carried out may vary within a very wide range; good results are obtained when operating within the temperature range from 60° to 150°C and preferably in the range from 85° to 100°C. In this temperature range the polyphosphoric acid is sufficiently fluid to allow a good course of the reaction, with sufficiently high reaction speeds and with good yields.

Although the molar ratio between the cycloalkancarboxylic acid and the aromatic hydrocarbon may vary within wide limits, good results are obtained by operating with molar ratios ranging from 0.1:1 to 10:1 but preferably from 0.3:1 to 0.4:1.

The quantity of polyphosphoric acid to be used in the process according to this invention, expressed in moles of phosphoric anhydride per mole of cycloalkanecarboxylic acid varies from a minimum of one mole to a maximum of 10 moles, and is preferably around 5 moles.

It has been established that the duration of the reaction may vary, according to the reactivity of the cycloalkancarboxylic acid and of the aromatic hydrocarbon, between 30 minutes and six hours.

It has been found to be convenient to carry out the separation of the ketone from the reaction mass by means of extraction by heat of the reaction mass itself with a solvent such as for instance the same aromatic hydrocarbon used in the reaction, or by diluting the reaction mass with water and subsequently extracting with a solvent. Whatever way is followed, the organic extract contains, besides the ketone produced by the reaction, also the cycloalkanecarboxylic acid which has not reacted; this latter may be easily recovered from the organic extract by known methods, such as for instance the extraction by means of aqueous alkaline solutions and subsequent acidifying.

A further procedure for suitably effecting the separation of unreacted cycloalkanecarboxylic acid consists in subjecting the organic extract to fractional distillation under vacuum so as to obtain the solvent, the cycloalkanecarboxylic acid and the ketone separately.

By operating as described above, it is possible to recover from the inorganic residual phase the polyphosphoric acid used in the reaction and to re-use it after the total P_2O_5 content has been brought back to the desired value according to the known methods including heat-concentration of polyphosphoric acid or addition of the calculated amount of phosphoric anhydride as specified above. This allows an easy continuous execution of the process, which therefore is particularly suited for being conveniently applied on an industrial scale.

The yields in cycloalkylarylketones obtainable by the process according to this invention, vary between 90—100% of the theoretical calculated with respect to the converted cycloalkanecarboxylic acid.

It has been found that the ketones obtainable by the process according to this invention from cycloalkanecarboxylic acids and aromatic hydrocarbons having alkyl-substituents, show structural formulae of different types depending on the number and positions of said alkyl-substituents.

When aromatic hydrocarbons mono-substituted with alkyl groups, such as toluene, ethylbenzene, cumene, etc.; or aromatic hydrocarbons disubstituted by alkyl groups in the 1-and 3-positions, such as for instance m.xylene; or aromatic hydrocarbons tri-subtituted with alkyl groups in the 1,3, and 5-positions such as for instance 1,3,5-trimethylbenzene are used, the carbonyl group occupies the 4-position.

When aromatic hydrocarbons disubstituted by alkyl groups in the 1- and 4-positions are used, the carbonyl group takes the otho position with respect to one of the alkyl-substituents. When aromatic hydrocarbons trisubstituted with alkyl groups in the 1,3, and 4-positions are used the carbonyl group takes up position 6.

The ketones obtainable by the process subject of the present invention, are useful intermediates for pharmaceutical products, and for monomers from which originate plastic fibres and materials.

The following examples describe the present invention in more detail without limiting the invention over that defined in the appended claims.

Example 1

Into a 250 cc flask provided with a stirrer, a thermometer and a reflux condenser were introduced. 13.8 gms hexahydrobenzoic acid, 30 cc toluene and 70 gms. of polyphosphoric acid having a total content of 85% of phosphoric anhydride. The mixture was then heated under vigorous stirring, at 100°C for 6 hrs. The reaction mass was allowed to cool down to room temperature and was then treated with 100 cc. of iced-water. Thereupon the whole was extracted repeatedly with ether and the ether extracts gathered together were then washed 3 times with 10 cc. of a 10% sodium hydroxide aqueous solution. (In the alkaline extract there were found by titration, 0.21 gms. of unreacted hexahydrobenzoic acid).

The ether solution was then dried over

anhydrous sodium sulphate and the ether was evaporated in a water bath. After having eliminated by evaporation under vacuum the last traces of solvent, mainly consisting of excess toluene, there were obtained, as a slightly yellow crystalline residue, 19.8 gms. of cyclohexyl-p.-tolyl-ketone (corresponding to a yield of 92.5% calculated with respect to the converted hexahydrobenzoic acid).

Successively by distillation under vacuum, 17.5 gms. of pure cyclohexyl-p-tolyl-ketone with a boiling point of 97°—100° C/0.15 mm Hg and a melting point of 65°—66° C, were obtained.

Of that product an oxime was prepared which showed a melting point of 168°C, which was in good agreement with the value recorded by the technical literature.

Example 2

In the same apparatus as that described in example 1, were introduced 13.8 gms. of hexahydrobenzoic acid, 66 cc. of toluene and 70 gms. of polyphosphoric acid having a total content of phosphoric anhydride of 85%. The whole mixture was then heated up at 85°C for 6 hrs under simultaneous constant vigorous stirring. The reaction mass was then left to cool down to room temperature, was treated with 100 cc. iced water and finally repeatedly extracted with ether. The ether extracts gathered together were washed three times with 10 cc aqueous solution at 10% of sodium hydroxide. (From the alkaline extract, after acidification with diluted hydrochloric acid, extraction with ether and evaporation of the solvent, 2.73 gms. of unreacted hexahydrobenzoic acid were obtained).

The etheric extracts dried over anhydrous sodium sulphate, were concentrated by water bath and, after removal of the last traces of solvent by evaporation under vacuum, 16.6 gms. of cyclohexyl-p-tolyl-ketone were obtained as a slightly yellow solid crystalline residue. The yield, calculated with respect to the converted hexahydrobenzoic acid was 95.6%. By distillation under vacuum the raw product yielded 15.4 gms. of pure cyclohexyl-p-tolyl-ketone having a boiling point of 113°—115°C/2 mm Hg and a melting point of 66°C.

Example 3

In an apparatus similar to that described in the preceding examples, a mixture of 13.8 gms. of hexahydrobenzoic acid, 4.5 gms. of polyphosphoric acid (with a total content of P_2O_5 of 76%) and 60 cc. of toluene was heated at 115°C for 6 hrs.

The still hot reaction mass was poured into an extractor for liquids and extracted with toluene. The toluene solution thus obtained was washed three times with 20 cc. of a 10% aqueous solution of sodium hydroxide. (In the alkaline extracts were found by titraction 3.4 gms. of unreacted hexahydrobenzoic acid.)

The toluene-extracts gathered together were dried over anhydrous sodium sulphate and then concentrated to dryness by evaporation under vacuum of the solvent. 13.7 gms. of slightly brownish cyclohexyl-p-tolyl-ketone were obtained as a residue.

The yield in cyclohexyl-p-tolyl-ketone, calculated with respect to the converted hexahydrobenzoic acid, turned out to be of 83.5%.

Example 4

Operating as described in the preceding examples, a mixture was made to react for 6 hrs, at 80—85°C, this mixture consisting of 13.8 gms. of hexahydrobenzoic acid, 30cc. benzene and 70 gms. of polyphosphoric acid (total contents in P_2O_5=80%). In the alkaline extracts were found 10.2 gms. of hexahydrobenzoic acid which had not reacted, while from the ether extracts were obtained 5 gms. of residue which, after distillation under vacuum, yielded 3.9 gms. of cyclohexyl-phenyl-ketone having a boiling point of 165°—166°C/20 mm Hg and a melting point of 52°—53°C.

Example 5

Still operating according to the preceding examples, 13.8 gms. of hexahydrobenzoic acid, 35 cc. of p-xylene and 70 gms. of polyphosphoric acid (with a total contents in P_2O_5 of 85%) were made to react for 6 hrs. at 100°C.

In the alkaline extracts were found 4.7 gms. of unreacted hexahydrobenzoic acid. By concentrating the etheric extracts there was obtained as a solid residue, 12.2 gms. of cyclohexyl - (2.5 - dimethyl-phenyl) - ketone which showed the following elementary analysis:

found	C%=84.9	H%=9.7
calculated for $C_{15}H_{20}O$:	C%=83.3	H%=9.3

The yield in ketone as calculated with respect to the converted hexahydrobenzoic acid was 79.4%.

7.1 gms. of this product yielded by distillation under vacuum 5.3 gms. of pure cyclohexyl-(2.5 dimethyl-phenyl)-ketone having a boiling point of 113°—115° C/0.2 mm Hg and a melting point of from 43°—44°C.

The product showed, furthermore, the following elementary analysis:

found: C%=84.0 and H=9.6

The infrared absorption spectrum showed the following characteristics maxima (expressed in microns ±0.02):

5.93; 6.70; 8.58; 11.15; 11.33; 12.28; 12.74

The measurements were taken in KBr

tablets. From the cyclohexyl-(2.5 dimethyl-phenyl)-ketone obtained as above described, was prepared the corresponding oxime. This latter, crystallized from a benzol-petroleum-ether mixture, melted at 152—153°C and showed the following elementary analysis:

found: C%=78.5; H%=9.6; N%=5.8
calculated for $C_{15}H_{21}NO$=C%=77.8; H%=9.2; N%=6.0

Example 6

In the same apparatus and with the same procedures as described in example 1, 13.8 gms. of hexahydrobenzoic acid, 35cc ethylbenzene and 70 gms. of polyphosphoric acid (with a total content of phosphoric anhydride of 85%), were made to react under vigorous stirring for 6 hrs at 100°C.

In the alkaline extracts were found 3.8 gms of unreacted hexahydrobenzoic acid.

By concentration of the ether extracts there was obtained, as a solid residue, 14.1 gms. of cyclohexyl-(4-ethyl-phenyl)ketone showing the following elementary analysis:

found	C%=84.0	H%=9.8
calculated for $C_{15}H_{20}O$	C%=83.3	H%=9.3

The yield, calculated with respect to the unreacted hexahydrobenzoic acid, amounted to 83.5%. 8.3 gms. of the product provided by distillation, 7.2 gms. of pure cyclohexyl (4-ethylphenyl)-ketone having a boiling point=123°—126° C/0.4 mm Hg. and a melting point=50—51°C and showing the following elementary analysis:
found: C%=84.2 H%=9.5
The I.R. absorption spectrum showed the following characteristic maxima (expressed in microns ±0.02): 6.00; 6.23; 6.37; 7.98; 8.23; 8.42, 8.52; 10.52; 11.65; 11.91.
The measurement was carried out in KBr tablets. From the cyclo-hexyl-(4-ethyl phenyl)-ketone was prepared the oxime which, crystallized from a benzol-petroleum ether mixture, melted at 143°—144°C and showed the following elementary analysis:

found	C%=77.9	H%=9.4	N%=6.2
calculated for $C_{15}H_{21}NO$	C%=77.8	H%=9.2	N%=6.0

Example 7

In the same apparatus and with the same procedure as described in example 1, 13.8 gms of hexahydrobenzoic acid, 35cc m-xylene and 70 gms. of polyphosphoric acid (having a total contents in phosphoric anhydride of 85%) were heated at 100°C for 3 hrs.

From the alkaline extracts were recovered 0.85 gms. of hexahydrobenzoic acid. From the ether extracts were obtained by evaporation of the solvent 18.1 gms. of liquid residue. By distillation under vacuum pure cyclohexyl-(2.4 dimethyl-phenyl)-ketone having a boiling point of 105—107° C/0.15 mm Hg. and a refraction index n_D^{20}=1.5370, was obtained, the elementary analysis being the following:

found	C%=84.1	H%=9.4
calculated for $C_{15}H_{20}O$	C%=83.3	H%=9.3

The I.R. absorption spectrum showed the following characteristic maxima (expressed in microns ±0.02): 5.95; 6.20; 6.39; 8.02; 8.29; 10.25; 12.18; 12.46; 12.82.

Example 8

In the same apparatus and with the same procedure as described in example 1, 13.8 gms. of hexahydrobenzoic acid, 40 cc cumene and 70 gms of polyphosphoric acid (having a total contents in phosphoric anhydride of 85%) were heated at 100°C for 6 hrs.

From the alkaline extracts were recovered 2.5 gms of hexahydrobenzoic acid. From the ether extracts, by evaporation of the solvent were obtained 11.9 gms. of liquid residue which, by distillation under vacuum, yielded pure cyclohexyl-(4-isopropyl-phenyl)-ketone, having a boiling point of 120°—125° C/0.3 mm Hg, a refraction index n_D^{20}=1.5334 and showing the following elementary analysis:

found	C%=83.2	H%=9.7
calculated for $C_{16}H_{22}O$	C%=83.4	H%=9.6

From this product was prepared the oxime which, crystallized from a benzol-petroleum ether mixture, showed a melting point of 163°—164°C and the following elementary analysis:

found	C%=78.9	H%=9.6	N%=5.5
calculated for $C_{16}H_{23}NO$	C%=78.3	H%=9.45	N%=5.7

EXAMPLE 9

With the same apparatus and following the same procedures as those described in example 1, 20 gms. of cyclo-octanecarboxylic acid, 36 cc toluene and 80 gms. of polyphosphoric acid (with a total content in P_2O_5 of 85%) were heated at 100°C for 3.5 hrs.

From the alkaline extracts were recovered 1.4 gms. of cyclooctanecarboxylic acid.

From the ether extracts were obtained by evaporation of the solvent 31 gms. of an oily residue from which, by distillation under vacuum, 26 gms. of cyclooctyl-p-tolyl-ketone were obtained, having a boiling point 140°—145° C/0.5 mm Hg, a refraction index $n_D^{20}=1.5481$ and showing the following elementary analysis:

found	C%=83.4	H%=9.1
calculated for $C_{16}H_{22}O$	C%=83.4	H%=9.6

The infrared absorption spectrum showed the following characteristic maxima (expressed in micron ±0.02) 5.95; 6.22; 6.36; 8.47; 8.95 and the following maxima referable to the cycloalkyl group:
6.8; 6.9; 7.1; 7.25; 7.32

From the cyclooctyl-p-tolyl-ketone was prepared the oxime which crystallized from a benzol-petroleum ether mixture, melted at 148°—150°C and showed the following elementary analysis:

found for	C%=79.0	H%=9.3	N%=6.1
calculated from $C_{16}H_{23}NO$	C%=78.3	H%=9.45	N%=5.7

EXAMPLE 10

With the same procedure and apparatus described in the preceding examples, a mixture consisting of 13.6 gms. of cyclododecanecarboxylic acid, 18 cc toluene and 40 gms. polyphosphoric acid (having a total content in phosphoric anhydride of 85%). was heated at 100°C for 4 hrs. From the alkaline extracts were recovered 6.7 gms. of cyclododecanecarboxylic acid. From the ether extracts, by evaporation of the solvent, was obtained as a residue a crystalline product mixed with traces of an oily product weighing 7.6 gms. which, subjected to distillation under vacuum, yielded 5.1 gms. of cyclododecyl-p-tolylketone having a boiling point of 168°—171° C/0.3 mm Hg and, after crystallization from petroleum ether, a melting point of 65°—65°C. The resulting product showed the following elementary analysis:

found	C%=83.9	H%=10.2
calculated for $C_{20}H_{30}O$	C%=83.8	H%=10.5

The infrared absorption spectrum showed the following characteristic maxima (expressed in micron ±0.02): 5.96; 6.23; 6.37; 8.05; 8.34; 8.46; 8.56; 12.92; 13.75; 13.92
The measurement was effected in KBr tablet.

WHAT WE CLAIM IS:—

1. A process for preparing cycloalkyl aryl ketones in which an aromatic hydrocarbon is reacted with a cycloalkane carboxylic acid in the presence of polyphosphoric acid having a total content of phosphoric anhydride between 73 and 88% by weight, at such a temperature that the polyphosphoric acid is to some extent fluid and at a molar ratio between P_2O_5 and cycloalkane carboxylic acid of between 1:1 and 10:1.

2. A process as claimed in claim 1 in which the polyphosphoric acid has a total content of phosphoric anhydride between 80% and 85% by weight.

3. A process as claimed in claim 3 in which the molar ratio is about 5:1.

4. A process as claimed in any one preceding claim when carried out at a temperature between 60° and 150°C.

5. A process as claimed in claim 5 when carried out at a temperature between 85° and 100°C.

6. A process as claimed in any one preceding claim when carried out at a molar ratio between the cycloalkane carboxylic acid and the aromatic hydrocarbon of from 0.1:1 and 10:1.

7. A process as claimed in claim 7 in which the ratio lies between 0.3:1 and 0.4:1.

8. A process as claimed in any one preceding claim when carried out for between 30 minutes and six hours.

9. A process as claimed in any one preceding claim where the cycloalkane ring contains from 4 to 12 carbon atoms.

10. A process as claimed in claim 1 in which the carboxylic acid is one of cyclopentanecarboxylic acid, hexahydrobenzoic acid, cyclooctanecarboxylic acid, cyclohendecane-carboxylic acid, cyclododecanecarboxylic acid, or the alkyl derivatives thereof.

11. A process as claimed in any one preceding claim in which the aromatic hydrocarbon is benzene or a benzene substituted with one or more alkyl groups.

12. A process as claimed in claim 12 in

which the aromatic hydrocarbon is toluene, a xylene, ethylbenzene, or cumene.

13. A process as claimed in any one preceding claim in which the polyphosphoric acid is prepared by prolonged heating of orthophosphoric acid until the desired concentration of phosphoric anhydride is reached.

14. A process as claimed in any one of claims 1 to 13 in which the polyphosphoric acid is prepared by dissolving the requisite amount of phosphoric anhydride in orthophosphoric acid.

15. A process as claimed in any one preceding claim in which the reaction mass formed is intracted, with a further portion of the aromatic hydrocarbon used as a solvent, under the influence of the heat of the reaction mass.

16. A process as claimed in any one of claims 1 to 16. in which the reaction mass formed is diluted with water before being extracted with a solvent.

17. A process as claimed in any one preceding claim in which polyphosphoric acid is recovered from the reaction mass and re-used for a subsequent run after its phosphoric anhydride content has been restored to the desired level.

18. A process for preparing cycloalkyl aryl ketones substantially as herein described with reference to any one of the Examples given.

19. Cycloalkyl aryl ketones produced by the process as claimed in any one preceding claim.

MARKS & CLERK
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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patent No. 940,255.

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